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Mendelian Randomization Dairy Cons

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Dairy Consumption and Body Mass Index Among Adults: Mendelian Randomization Analysis of 184 802 Individuals from 25 Studies

Mendelian Randomization of Dairy Consumption Working Group

BACKGROUND: Associations between dairy intake and body mass index (BMI) have been inconsistently observed in epidemiological studies, and the causal relationship remains ill defined.

METHODS: We performed Mendelian randomization (MR) analysis using an established dairy intake-associated genetic polymorphism located upstream of the lactase gene (*LCT*-13910 C/T, rs4988235) as an instrumental variable (IV). Linear regression models were fitted to analyze associations between (a) dairy intake and BMI, (b) rs4988235 and dairy intake, and (c) rs4988235 and BMI in each study. The causal effect of dairy intake on BMI was quantified by IV estimators among 184 802 participants from 25 studies.

RESULTS: Higher dairy intake was associated with higher BMI ($\beta = 0.03 \text{ kg/m}^2$ per serving/day; 95% CI, 0.00–0.06; $P = 0.04$), whereas the *LCT* genotype with 1 or 2 T allele was significantly associated with 0.20 (95% CI, 0.14–0.25) serving/day higher dairy intake ($P = 3.15 \times 10^{-12}$) and 0.12 (95% CI, 0.06–0.17) kg/m^2 higher BMI ($P = 2.11 \times 10^{-5}$). MR analysis showed that the genetically determined higher dairy intake was significantly associated with higher BMI ($\beta = 0.60 \text{ kg/m}^2$ per serving/day; 95% CI, 0.27–0.92; $P = 3.0 \times 10^{-4}$).

CONCLUSIONS: The present study provides strong evidence to support a causal effect of higher dairy intake on increased BMI among adults.

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The prevalence of obesity has been rapidly increasing over the world and is paralleled by a historic shift of lifestyle from traditional healthy patterns toward unhealthy patterns (1). However, the causal relationships

between lifestyle factors and obesity have yet to be fully elucidated.

A body of observational epidemiologic studies investigating the association between dairy intake and weight status has reported inconsistent results. A recent systematic review of prospective cohort studies showed a negative association of dairy consumption with risk of overweight and obesity, but considerable heterogeneities existed (2), making definitive conclusions difficult. Metaanalyses of randomized controlled trials (RCTs)⁷⁴ suggest that dairy consumption may not influence body weight when all the participants are analyzed, but it may reduce body weight and fat mass in the context of energy restriction (3–6). However, because of the relatively short duration of intervention (often <1 years) and the special populations often evaluated (e.g., obese individuals seeking weight loss), the effects of habitual dairy intake on body weight in general populations remain unclear.

Mendelian randomization (MR) analysis has become widely used to assess potential causal relations of environmental risk factors and diseases (7). This method is analogous to an RCT in which randomization to genotype takes place at conception (8, 9). In our recent MR analysis, we demonstrated that dairy intake was not causally related to hypertension, using an established dairy intake-associated genetic variant near the lactase gene *LCT*⁷⁵ (10). In the current study, we performed the largest MR analysis thus far among 184 802 adult participants from 25 cohorts to examine the causal relationship between habitual dairy intake and body weight in general populations.

Methods

STUDY DESIGN

The study design consisted of 2 steps. First, using cross-sectional and prospective cohort studies, we tested the

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⁷⁴ Nonstandard abbreviations: RCT, randomized controlled trial; MR, Mendelian randomization; BMI, body mass index; IV, instrumental variable.

⁷⁵ Human Genes: *LCT*, lactase; *MCM6*, minichromosome maintenance complex component 6.

dairy intake-associated *LCT*-13910 C/T, rs4988235 for association with dairy intake and body mass index (BMI). Second, the causal effect of dairy intake on BMI was quantified with instrumental variable (IV) estimators among 184802 participants from 25 studies.

STUDY PARTICIPANTS

The study was conducted within the Mendelian Randomization of Dairy Consumption Working Group, represented here by 25 cohort studies and up to 184802 individuals (see Table 1 in the Data Supplement that accompanies the online version of this article at <http://www.clinchem.org/content/vol64/issue1>). Descriptions of each participating study are shown in Table 2 of the online Data Supplement. Participants from all participating studies provided written informed consent, and ethical approval was granted by local institutional review boards (see Table 3 in the online Data Supplement). Intake of dairy products was collected by self-reported questionnaire in each study; detailed information on cohort-specific data collection methods is provided in Table 4 of the online Data Supplement. Total dairy products included skim/low fat milk, whole milk, ice cream, yogurt, cottage/ricotta cheese, cream cheese, other cheese, and cream.

The primary outcome is follow-up BMI or baseline BMI, calculated as weight in kilograms divided by the square of height in meters. Height and body weight were directly measured in some studies and self-reported in others. Detailed information on the outcome measure for each study is reported in Table 5 of the online Data Supplement.

SINGLE-NUCLEOTIDE POLYMORPHISM SELECTION AND GENOTYPE PROPERTIES

The *LCT*-13910 C/T polymorphism (rs4988235), located upstream from the *LCT* gene, affects the transcription of the lactase enzyme and is associated with lactase persistence and thereby with the ability to digest lactose, the primary source of carbohydrates in milk (11). Lactase persistence is a dominantly inherited genetic trait. The TT and TC genotypes are associated with lactase persistence, and the CC genotype is associated with nonpersistence. In the present study, we chose the widely confirmed and extensively studied variant rs4988235 as the IV for dairy intake (12–14). Twenty studies used direct genotype information on rs4988235 from previously genotyped array data. Whenever rs4988235 was not genotyped directly, we used either (a) the HapMap II CEU (European) reference panel-imputed genetic information from genome-wide association studies (http://hapmap.ncbi.nlm.nih.gov/downloads/genotypes/2008-10_phaseII/) for rs4988235 or (b) genotype information from a predefined list of proxies that are in high linkage disequilibrium with rs4988235 ($n = 5$, $r^2 > 0.9$). Genotyping platforms, genotype frequencies, Hardy–

Weinberg equilibrium P values, and call rates (median of 98.8%) for *LCT*-13910 C/T are listed in Tables 1 and 6 of the online Data Supplement.

STATISTICAL ANALYSIS

A standard analysis protocol was applied to each individual study to produce comparable results. As lactase persistence is a dominantly inherited genetic trait, we examined the genetic association primarily under a dominant model (CC vs CT + TT). We also applied an additive model and recessive model (CC + CT vs TT) to examine the genetic association of *LCT*-13910 C/T with dairy intake and BMI. Linear regression was used to test the association of dairy intake with BMI after adjustment for age, sex, ethnicity, region, years of follow-up, and other baseline covariates (smoking status, physical activity, total energy intake, and alcohol intake), as available. Linear regression was used to test the association of *LCT*-13910 C/T with dairy intake or BMI after adjustment for age, sex, ethnicity, region, and total energy. Table 5 in the online Data Supplement shows the BMI outcome information.

METAANALYSIS AND BETWEEN-STUDY HETEROGENEITY

Metaanalyses were conducted using individual participant data in each study and then pooled β coefficients across studies using random-effects or fixed-effects meta-analysis. Metaanalyses were conducted in Stata version 13.0 (StataCorp, www.stata.com). All P values reported were 2-sided. We assessed between-study heterogeneity via Cochran's Q and I^2 statistics (15–17). For the proposed cutoff of $I^2 > 0.25$, we found nonnegligible heterogeneity between studies, in particular among the dairy–BMI associations, but also for the association between *LCT*-13910 C/T and dairy intake ($I^2 = 0.55$). As a consequence, we used random-effects metaanalysis throughout. Furthermore, metaregression was used to investigate the extent to which statistical heterogeneity between results of studies could be related to 1 or more characteristics of the studies.

SE AND INFERENCE FOR THE IV ESTIMATOR

After metaanalysis, we used the IV estimator to quantify the strength of the causal association of dairy intake and BMI (18). The IV estimator was calculated as the β of the regression coefficients for *LCT*-13910 C/T–BMI and *LCT*-13910 C/T–dairy and is identical to that derived by the widely used 2-stage least-squares method (19) (see Material section in the online Data Supplement).

Results

BASELINE CHARACTERISTICS OF PARTICIPATING STUDIES

Baseline characteristics of the 184802 participants from 25 studies are shown in Table 1 here and in Table 1 of the

Table 1. Baseline characteristics of participating studies.

Studies	Sample size	Study design	Baseline year	Follow-up time, year	Age, year	BMI, kg/m ²
ARIC-AA	1889	Cohort	1987	5.8	53.2 ± 5.7	29.7 ± 5.9
ARIC-EA	8233	Cohort	1987	6	54.3 ± 5.6	27.0 ± 4.7
BPHRS ^a	845	Cohort	2003	2.4	57.0 ± 8.0	32 ± 7.0
CCHS	8702	Cohort	1991-1994	20	60.0 ± 8.0	25 ± 4.0
CGPS ^a	74 128	Cohort	2003-2011	5.7	57.0 ± 8.0	25.6 ± 4.0
CHS	1943	Cohort	1989-1990	8.9	71.1 ± 4.3	26.4 ± 4.2
DESIR	3468	Cohort	1994-1996	9	47.2 ± 9.9	24.6 ± 3.6
DCH	1297	Nested cohort	1993-1997	5	55.9 ± 4.4	25.2 ± 3.5
Diogenes-C	1002	Nested case-cohort	1993-1997	5	53.6 ± 2.60	25.5 ± 3.6
Diogenes-W	813	Nested case-cohort	1993-1997	5	53.4 ± 2.6	26.9 ± 4.0
FamHS	2167	Family-based cohort	1992	7.9	50.6 ± 10.0	28.8 ± 5.0
GESUS ^a	14 751	Cohort	2010-2013	2.1	56.0 ± 4.0	26.1 ± 4.0
GLACIER	3129	Cohort	1991-2001	9.9	45.2 ± 6.7	25.1 ± 3.7
GOLDN ^a	818	Cohort	—	0	49.0 ± 1.06	28.0 ± 5.0
HPFS	7599	Cohort	1990	10	57.7 ± 11.8	25.9 ± 3.3
INCH ^a	647	Cohort	1998	8.7	63.4 ± 14.8	27.1 ± 4.0
Inter99	6161	Cohort	1999	5	46.2 ± 7.9	26.3 ± 4.6
MDCS	3199	Cohort	1991-1996	16.7	56.3 ± 5.7	25.4 ± 3.7
MESA	2423	Cohort	1990	10	60.7 ± 9.6	28.2 ± 5.2
NHS	12 039	Cohort	1990	10	57.3 ± 9.6	26.2 ± 5.2
PREDIMED-Valencia	940	Cohort	2003	2	67.0 ± 7.0	30.1 ± 4.2
RAINE	730	Cohort	2010	2.1	19.9 ± 0.3	24.3 ± 5.1
RS	3215	Cohort	1990	6.5	65.8 ± 6.8	26.3 ± 3.5
WGHS	23 294	Cohort	1992	2	54.2 ± 7.1	25.9 ± 4.9
YFS	1370	Cohort	1980	4	38.1 ± 4.0	25.8 ± 5.0

^a Data were analyzed cross-sectionally.
ARIC-AA, ARIC (African Ancestry); ARIC-EA, ARIC (European Ancestry).

online Data Supplement. A description of each study and additional characteristics of participants are presented in Tables 1 through 6 of the online Data Supplement. Twenty studies provided data for *LCT*-13910 C/T, and 5 studies provided results for the proxy single-nucleotide polymorphism (defined on the basis of $r^2 \geq 0.90$ with rs4988235 in individuals; see Table 6 in the online Data Supplement). Findings from χ^2 tests showed that the CCHS, CGPS, FamHS, and GLACIER did not achieve Hardy–Weinberg equilibrium (see Table 6 in the online Data Supplement).

DAIRY INTAKE AND BMI

Random-effects metaanalysis was used to pool the association between dairy intake and BMI in the 176 100 participants from 24 studies. We observed that high dairy intake was significantly associated with higher BMI ($\beta = 0.03$ kg/m² per serving/day; 95% CI, 0.00–0.06; $P =$

0.04). The β coefficient estimates of effect sizes for the association between dairy intake and BMI ranged from -0.18 to 0.20 kg/m² per serving/day of dairy intake, yielding an I^2 for heterogeneity between studies of 79.7% (Fig. 1). Metaregression analysis showed that age significantly influenced the association of dairy consumption with BMI ($P = 0.02$). Stratified analysis by age showed that dairy consumption was significantly associated with higher BMI among participants >50 years ($\beta = 0.05$ kg/m² per serving/day; 95% CI, 0.02–0.07) but tended to be associated with lower BMI among participants <50 years ($\beta = -0.04$ kg/m² per serving/day; 95% CI, -0.11 to 0.03).

GENETIC ASSOCIATION OF *LCT*-13910 C/T WITH DAIRY INTAKE AND BMI

Random-effects metaanalysis, with a dominant model, was used to pool the genetic association of the *LCT*-

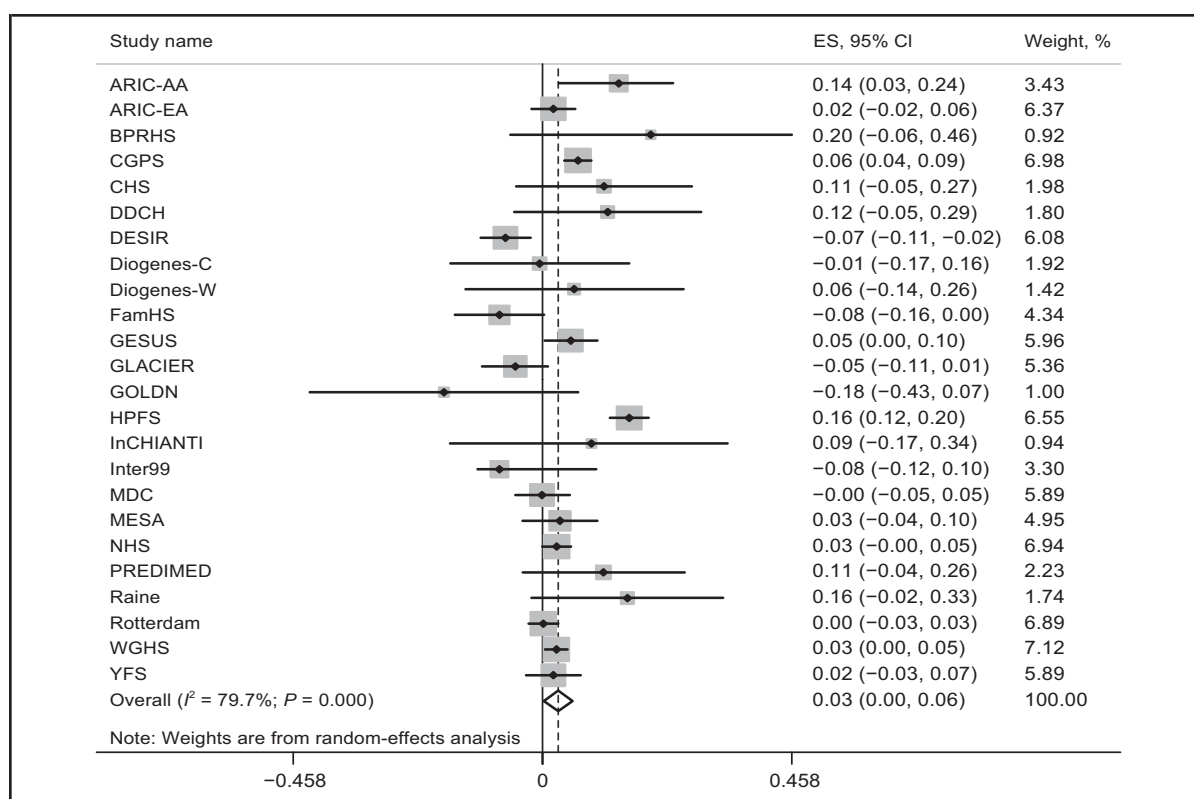


Fig. 1. Association between dairy intake and BMI among 176 100 participants from 24 studies.

Linear regression was used to test the association of dairy intake (serving/day) with BMI (kg/m^2) after adjustment of sex, ethnicity, region, years of follow-up, and other baseline covariates if available (age, smoking status, physical activity, total energy intake, and alcohol intake) in each study. We pooled β coefficients across 24 studies using random-effects metaanalysis because of the heterogeneity between studies ($I^2 = 79.7\%$; $P < 0.001$). ARIC-AA, ARIC (African Ancestry); ARIC-EA, ARIC (European Ancestry); PREDIMED, PREDIMED-Valencia; ES, effect size.

13910 C/T with dairy intake in the 176 100 participants from 24 studies ($I^2 = 83.0\%$). We found that the *LCT*-13910 C/T CT + TT genotype was significantly associated with 0.20 more dairy servings per day ($\beta = 0.20$ serving/day; 95% CI, 0.14–0.25; $P = 3.15 \times 10^{-12}$). We also pooled the genetic association with BMI in the 184 802 participants from 25 studies using fixed-effects metaanalysis ($I^2 = 14.4\%$; $P = 0.258$) and found that the *LCT*-13910 C/T CT + TT genotype was significantly associated with 0.12 higher BMI unit (kg/m^2) ($\beta = 0.12$; 95% CI, 0.06–0.17; $P = 2.11 \times 10^{-5}$) (Fig. 2).

In sensitivity analyses, we found similarly significant genetic associations of *LCT*-13910 C/T with dairy intake ($\beta = 0.09$ serving/day; 95% CI, 0.06–0.12; $P = 4.24 \times 10^{-9}$), and genetic association with BMI ($\beta = 0.09$ serving/day; 95% CI, 0.04–0.14; $P = 0.0003$) under the additive model (see Fig. 1 in the online Data Supplement). Significant genetic associations were also observed under the recessive model (see Table 7 in the online Data Supplement).

IV ESTIMATED CAUSALITY BETWEEN DAIRY INTAKE AND BMI

After we pooled estimated effect sizes from each study using metaanalysis, we used the IV estimators to quantify the strength of the causal association of dairy intake and BMI, with the *LCT*-13910 C/T used as an IV. The MR estimate was computed from the ratio of the coefficient of the association between the *LCT*-13910 C/T and BMI to that of the association between the *LCT*-13910 C/T and dairy intake. This IV estimate reflects the potential causal effect of dairy intake on BMI. Fig. 3 presents the observational association of dairy intake with BMI, as well as the IV estimated causal effect of dairy intake on BMI. The pooled results show that genetically higher dairy intake was significantly associated with higher BMI ($\beta = 0.60 \text{ kg/m}^2$ per 1 serving/day; 95% CI, 0.27–0.92; $P = 3.0 \times 10^{-4}$) under the dominant model. We also found evidence of significant causal association between dairy intake and BMI under the additive model ($\beta = 1.00 \text{ kg/m}^2$; 95% CI, 0.30–1.69; $P = 4.0 \times 10^{-3}$) and the recessive model ($\beta = 1.59 \text{ kg/m}^2$; 95% CI, 0.28–2.91; $P = 0.009$) (see Fig. 1 and Table 7 in the online Data Supplement).

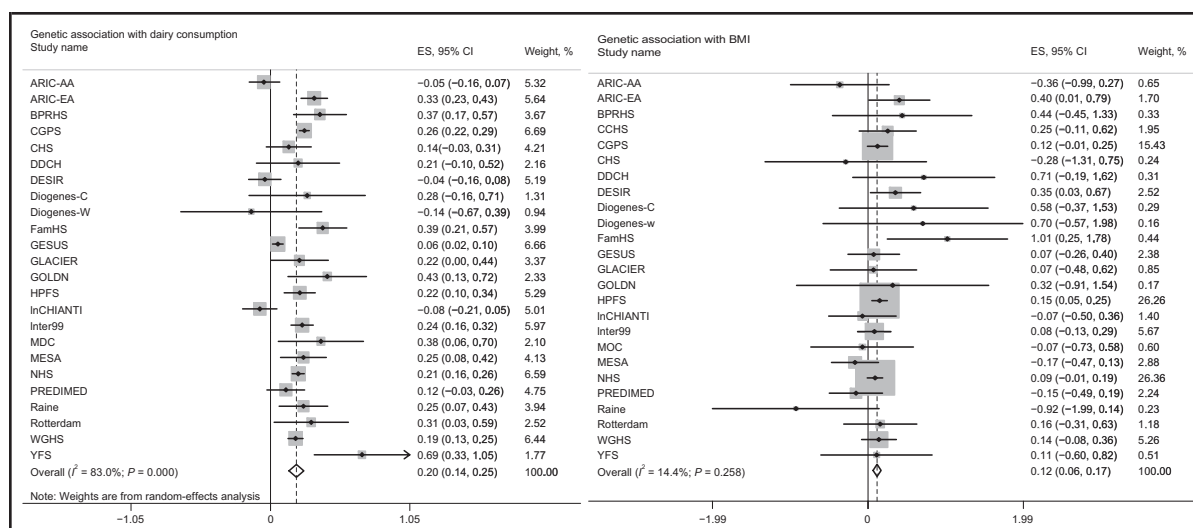


Fig. 2. Genetic association and estimated causality between dairy intake and BMI in dominant model.

The *LCT*-13910 C/T located upstream of the lactase (*LCT*) gene was selected as IV. The TT and TC genotypes are associated with lactase persistence, and the CC genotype is associated with nonpersistence. Random-effects metaanalysis was used to pool the genetic association with dairy intake in 176 100 participants from 24 studies because of the heterogeneity between studies ($I^2 = 83.0\%$). Fixed-effects metaanalysis was used to pool the genetic association with BMI association in 184 802 participants from 25 studies ($I^2 = 14.4\%$). PREDIMED, PREDIMED-Valencia; ES, effect size.

ment). We did not observe significant differences in observational results or IV estimated results ($P = 0.63$).

We further conducted stratified analyses of genetic association with dairy intake and BMI and estimated causality by age, BMI, follow-up years, sample size, study design, and ethnic group. Table 2 presents the genetic associations and the IV estimate for the association of dairy intake with BMI from overall and subgroup analyses. Genetic associations of the *LCT*-13910 C/T with

BMI and a causal effect of dairy intake on BMI were observed only among those of European ancestry and in studies with mean age ≥ 50 years, BMI ≥ 25 kg/m², follow-up time ≥ 5 years, and sample size ≥ 1000 .

Discussion

In thus far the largest MR analysis study, including 184 802 adults from 25 cohorts, our results support a

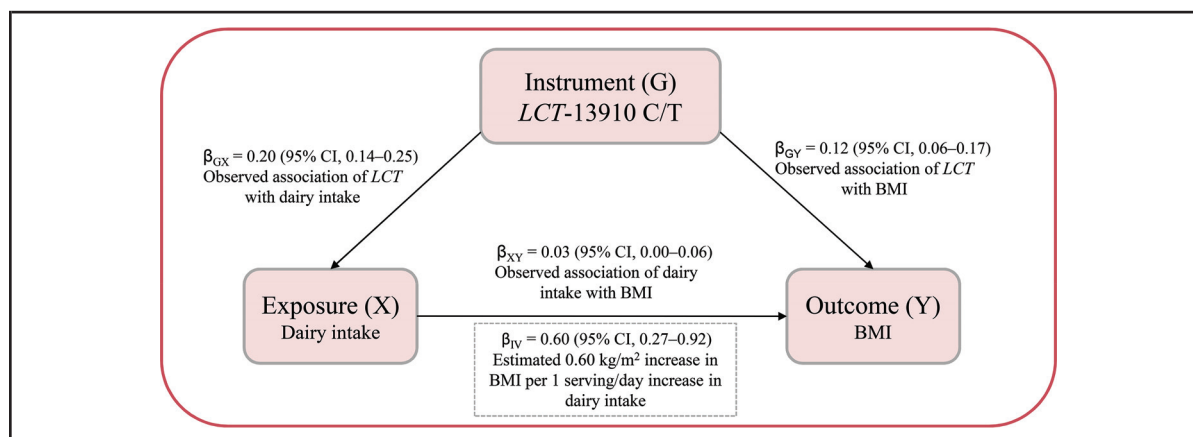


Fig. 3. MR triangulation for BMI.

The IV estimator was used to quantify the strength of the causal association of dairy intake with BMI using *LCT*-13910 C/T as IV.

Subgroup	Dairy (outcome), serving/day			BMI (outcome), kg/m ²			Estimated causality	
	Studies SNP (IV)			Studies SNP (IV)			Estimated causality	
	No.	β (95% CI)	P value	No.	β (95% CI)	P value	β (95% CI)	P value
Age, years								
≥50	19	0.19 (0.12–0.26)	<0.001	19	0.12 (0.05–0.19)	<0.001	0.64 (0.22–1.07)	<0.001
<50	5	0.35 (0.17–0.53)	<0.001	6	0.06 (–0.13 to 0.24)	0.513	0.16 (–0.38 to 0.69)	0.371
BMI, kg/m ²								
≥25	19	0.20 (0.14–0.27)	<0.001	19	0.11 (0.06–0.17)	0.001	0.55 (0.23–0.88)	<0.001
<25	5	0.21 (0.15–0.27)	<0.001	6	0.15 (–0.17 to 0.47)	0.147	0.68 (–0.83 to 2.20)	0.269
Follow-up, years								
≥5	13	0.20 (0.13–0.27)	<0.001	14	0.11 (0.03–0.19)	0.001	0.55 (0.09–1.00)	<0.001
<5	11	0.24 (0.13–0.36)	<0.001	11	0.13 (–0.01 to 0.26)	0.112	0.51 (–0.07 to 1.10)	0.074
Sample size								
≥1000	20	0.23 (0.17–0.29)	<0.001	21	0.12 (0.05–0.18)	<0.001	0.51 (0.19–0.83)	<0.001
<1000	4	0.21 (0.15–0.27)	<0.001	4	0.04 (–0.35 to 0.43)	0.912	0.18 (–1.63 to 2.00)	0.615
Ethnic group								
European	19	0.21 (0.15–0.28)	<0.001	20	0.13 (0.08–0.18)	<0.001	0.62 (0.30–0.93)	<0.001
Non-European	5	0.22 (0.04–0.41)	<0.001	5	–0.18 (–0.42 to 0.07)	0.611	–0.79 (–2.07 to 0.49)	0.662
Study design								
Cohort	19	0.20 (0.17–0.22)	<0.001	20	0.12 (0.06–0.17)	<0.001	0.60 (0.32–0.88)	<0.001
Cross-sectional	5	0.1 (0.13–0.19)	<0.001	5	0.11 (–0.01 to 0.22)	0.231	0.69 (–0.04 to 1.41)	0.06
HWE								
≤0.05	20	0.23 (0.16–0.28)	<0.001	21	0.12 (0.07–0.19)	<0.001	0.52 (0.18–0.82)	<0.001
>0.05	4	0.21 (0.16–0.28)	<0.001	4	0.05 (–0.34 to 0.45)	0.753	0.19 (–1.57 to 1.76)	0.714

SNP, single-nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium.
 Linear regression was used to test the association of *MCM6* variant rs4988235 with dairy intake or BMI after adjustment of age, sex, ethnicity, region, total energy, and principal component for population stratification, as appropriate.
 We pooled β coefficients across studies using random-effect metaanalysis because of the heterogeneity between studies ($I^2 > 50\%$; $P < 0.001$).
 We used the IV estimators to quantify the strength of the causal association of dairy intake and BMI in each study. The IV estimator that is identical to that derived by the widely used 2-stage least-squares method will be calculated as the β of the regression coefficients *MCM6* rs4988235-BMI and *MCM6* rs4988235-dairy.

causal relation between higher dairy intake and increased BMI in the absence of caloric restriction.

A number of recent prospective cohort studies exploring the association between intake of dairy foods and weight status have generated inconsistent results (12, 20–22). Evidence from a systematic review showed that much confusion remains about this relationship (2). Possible reasons for such apparent inconsistencies in findings include varying sample sizes, residual and unmeasured confounding, and reverse causality because of changes in outcome and factors over time. In addition, 1 metaanalysis of RCTs showed that ad libitum dairy interventions in long-term trials might increase body weight (5). However, several RCTs with energy restriction reported opposing effects (5). Differences in dose of dairy, foods included as dairy, mode of administration, duration of intervention, energy restriction, or baseline differences in dairy intake or body weight between the trials may be prone to bias, undermining their validity.

Furthermore, the types of dairy products may also partly account for this apparent discrepancy. A limited number of studies have examined the impact of type of dairy product on body composition. In 1 metaanalysis study, both whole fat and low fat dairy food intervention significantly increased body weight (4). In addition, fermented milk products such as yogurt have shown beneficial effects in the control of body weight (23), whereas cheese intake has exhibited a positive association with obesity (24). Taken together, previous evidence makes definitive conclusions on the relation between dairy consumption and adiposity difficult.

Recently, genetic analysis has become widely used to infer causality of environmental factors on human disease (7). The MR analysis is a method that uses genetic variants that are robustly associated with such modifiable factors to generate more reliable evidence regarding which interventions should produce health benefits (25). The MR analysis is not prone to confounding or reverse

causation. It is well known that alleles that are randomly assigned at meiosis are independent of nongenetic confounding and are unmodified by health conditions. Therefore, MR is analogous to an RCT and can be used to support the hypothesis that the association of dairy intake with BMI is causal. Recently, a genetic analysis from the 1982 Pelotas (Brazil) Birth Cohort (26) did not support a causal relationship between high dairy intake and increased BMI. However, this study was limited by small sample size ($n = 2808$) and low power to derive valid conclusions. In our well-powered study, we individually analyzed 184 802 individuals from 25 cohorts and provide strong evidence that high dairy intake was causally associated with higher BMI. Results from our MR and multivariable analyses were highly consistent, both confirming higher BMI in those eating more dairy products.

The potential mechanisms underlying the impact of dairy intake on the regulation of body weight have not been clearly elucidated. The most postulated mechanism is that the hormone estrone found in dairy products may promote increases in body weight (20, 27). In addition, intake of dairy foods is associated with higher plasma insulin-like growth factor I, which may contribute to weight gain (28). Furthermore, previous studies suggested that extra dairy intake in ad libitum dietary interventions may lead to increased energy intake, which may result in weight gain, offsetting the otherwise potential protective effect of the dairy intervention (5). In contrast, in most energy-restricted trials, energy intakes were better controlled. Thus, the potential benefits of dairy on body weight could be interpreted as the effect of the substitution of dairy products for certain other foods (5). Therefore, total energy intake needs to be considered when assessing the role of dairy intake in weight control (3–6). In addition, metaanalysis of RCTs showed that dairy consumption increased lean (muscle) mass and decreased body fat (3). Increased protein intake from dairy products may promote maintenance of lean mass (6). Thus, in the present study, it is possible that the higher BMI related to high dairy intake could be mainly because of increased lean muscle mass. Future research is needed to further illustrate potential mechanisms of dairy products on body weight and composition in the context of energy restriction.

Our study has several strengths. First, to the best of our knowledge, this is thus far the largest MR analysis on the causality of high dairy intake on BMI. The large sample size allowed us to assess the consistency of associations across multiple studies and to gain sufficient power for conclusive estimation of causal effect. Second, the MR design used in our genetic analyses should have largely prevented potentially distorting influences. Third, the lactose-tolerance variant is a well-established genetic marker for dairy intake, with solid biological basis and, therefore, a valid IV for dairy intake (10, 13). Lastly,

most of the studies included were homogeneous, and we performed analysis individually in each study. Therefore, the effect of population stratification on the instrumental results should be minimal.

Potential limitations with the MR approach include the possibility of pleiotropy and population stratification. Pleiotropy refers to a situation in which a gene affects ≥ 2 apparently unrelated phenotypic traits; we could not exclude the possibility of pleiotropic effects of the *LCT* genotype. However, to our knowledge, no pleiotropic effect has been reported. Furthermore, the associations of rs4988235 with lactase persistence and milk intake vary across populations. We adjusted for only geographical region and ethnicity in the statistical models. Hence, bias from population stratification is deemed likely (29). Finally, although many important covariates were adjusted in our models, some residual and unmeasured confounding might remain.

Conclusions

In summary, the present study suggests a causal effect of higher dairy intake on increased BMI; our results also emphasize that total energy intake needs to be considered when assessing the role of dairy intake in weight control.

List of authors from the Mendelian Randomization of Dairy Consumption Working Group

Tao Huang,^{1,2,3,4†} Ming Ding,^{4†} Helle K.M. Bergholdt,^{5,6,7†} Tiange Wang,³ Yoriko Heianza,³ Dian-

¹ Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China; ² Epidemiology Domain, Saw Swee Hock School of Public Health, National University of Singapore, Singapore; ³ Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA; ⁴ Department of Nutrition, Harvard School of Public Health, Boston, MA; ⁵ Department of Clinical Biochemistry, Naestved Hospital, Naestved, Denmark; ⁶ Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ⁷ Department of Clinical Pharmacology, Copenhagen University Hospital Bispebjerg Frederiksberg, Copenhagen, Denmark; ⁸ USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX; ⁹ Department of Epidemiology, School of Public Health, University of Alabama, Birmingham, AL; ¹⁰ Department of Epidemiology, University of North Carolina, Chapel Hill, NC; ¹¹ Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands; ¹² Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA; ¹³ Department of Clinical Biochemistry and the Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Copenhagen, Denmark; ¹⁴ Department of Medicine, University of Washington, Seattle, WA; ¹⁵ INSERM, UMR S 1138, Centre de Recherche des Cordeliers, Paris, France; ¹⁶ University Paris Diderot, Sorbonne Paris Cité, UMR S 1138, Centre de Recherche des Cordeliers, Paris, France; ¹⁷ Sorbonne Universités, UPMC University Paris 06, UMR S 1138, Centre de Recherche des Cordeliers, Paris, France; ¹⁸ Department of Preventive Medicine and Public Health, University of Valencia, Valencia, Spain; ¹⁹ CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain; ²⁰ School of Women's and Infants' Health, The University of Western Australia, Crawley, WA, Australia; ²¹ Danish Cancer Society Research Center, Copenhagen, Denmark; ²² Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark; ²³ Aalborg University Hospital, Aalborg, Denmark; ²⁴ Novo Nordisk Foundation Center for Basic Metabolic Research, Section of

jianyi Sun,³ Alexis C. Frazier-Wood,⁸ Stella Aslibekyan,⁹ Kari E. North,¹⁰ Trudy Voortman,¹¹ Mariaelisa Graff,¹⁰ Caren E. Smith,¹² Chao-Qiang Lai,¹² Anette Varbo,^{6,13} Rozenn N. Lemaitre,¹⁴ M. Ester A.L. de Jonge,¹¹ Fré-

déric Fumeron,^{15,16,17} Dolores Corella,^{18,19} Carol A. Wang,²⁰ Anne Tjønneland,²¹ Kim Overvad,^{22,23} Thorkild I.A. Sørensen,^{24,25} Mary F. Feitosa,²⁶ Mary K. Wojczynski,²⁶ Mika Kähönen,^{27,28} Frida Renström,^{29,30} Bruce M. Psaty,^{31,32} David S. Siscovick,³³ Inês Barroso,^{34,35,36} Ingegerd Johansson,³⁷ Dena Hernandez,³⁸ Luigi Ferrucci,³⁹ Stefania Bandinelli,⁴⁰ Allan Linneberg,^{41,42} M. Carola Zillikens,⁴³ Camilla Helene Sandholt,²⁴ Oluf Pedersen,^{24,44} Torben Hansen,²⁴ Christina-Alexandra Schulz,⁴⁵ Emily Sonestedt,⁴⁵ Marju Orho-Melander,⁴⁵ Tzu-An Chen,⁸ Jerome I. Rotter,⁴⁶ Mathew A. Allison,⁴⁷ Stephen S. Rich,⁴⁸ Jose V. Sorlí,^{18,19} Oscar Coltell,^{19,49} Craig E. Pennell,²⁰ Peter Eastwood,⁵⁰ Albert Hofman,¹¹ Andre G. Uitterlinden,⁴³ Frank J.A. van Rooij,¹¹ Audrey Y. Chu,⁵¹ Lynda M. Rose,⁵¹ Paul M. Ridker,^{51,52} Jorma Viikari,^{53,54} Olli Raitakari,^{55,56} Terho Lehtimäki,^{57,58} Vera Mikkilä,^{56,59} Walter C. Willett,^{4,60,61} Yujie Wang,¹⁰ Katherine L. Tucker,⁶² Jose M. Ordovas,^{12,63,64} Tuomas O. Kilpeläinen,²⁴ Michael A. Province,²⁶ Paul W. Franks,^{4,29,65} Donna K. Arnett,⁶⁶ Toshiko Tanaka,³⁹ Ulla Toft,⁴¹ Ulrika Ericson,⁴⁵ Oscar H. Franco,¹¹ Dariush Mozaffarian,⁶⁷ Frank B. Hu,^{4,60,61} Daniel I. Chasman,^{51,68,69} Børge G. Nordestgaard,^{6,13,70†} Christina Ellervik,^{6,71,72†} and Lu Qi.^{3,4,73†}

Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ²⁵ Department of Public Health Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ²⁶ Department of Genetics, Washington University School of Medicine, St. Louis, MO; ²⁷ Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland; ²⁸ Department of Clinical Physiology Finnish Cardiovascular Research Center Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland; ²⁹ Genetic and Molecular Epidemiology Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; ³⁰ Department of Biobank Research, Umeå University, Umeå, Sweden; ³¹ Kaiser Permanente Washington Health Research Institute, Seattle, WA; ³² Cardiovascular Health Research Unit Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA; ³³ New York Academy of Medicine, New York, NY; ³⁴ NIHR Cambridge Biomedical Research Centre, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; ³⁵ University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; ³⁶ Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; ³⁷ Department of Odontology, Umeå University, Umeå, Sweden; ³⁸ Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD; ³⁹ Translational Gerontology Branch National Institute on Aging, Baltimore, MD; ⁴⁰ Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy; ⁴¹ Research Centre for Prevention and Health, the Capital Region of Denmark, Copenhagen, Denmark; ⁴² Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark; ⁴³ Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands; ⁴⁴ Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark; ⁴⁵ Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden; ⁴⁶ Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA; ⁴⁷ Division of Preventive Medicine, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA; ⁴⁸ Center for Public Health Genomics and Department of Public Health Sciences, University of Virginia, Charlottesville, VA; ⁴⁹ Department of Computer Languages and Systems, University Jaume I, Castellon, Spain; ⁵⁰ School of Anatomy, Physiology and Human Biology, The University of Western Australia, Western Australia, Australia; ⁵¹ Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; ⁵² Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; ⁵³ Division of Medicine, Turku University Hospital, Turku, Finland; ⁵⁴ Department of Medicine, University of Turku, Turku, Finland; ⁵⁵ Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland; ⁵⁶ Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; ⁵⁷ Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland; ⁵⁸ Department of Clinical Chemistry Finnish Cardiovascular Research Center Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland; ⁵⁹ Department of Food and Environmental Sciences, University of Helsinki, Helsinki, Finland; ⁶⁰ Department of Epidemiology, Harvard School of Public Health, Boston, MA; ⁶¹ Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; ⁶² Biomedical and Nutritional Sciences, Center for Population Health, University of Massachusetts Lowell, Lowell, MA; ⁶³ Department of Epidemiology and Population Genetics, Centro Nacional Investigación Cardiovasculares (CNIC), Madrid, Spain; ⁶⁴ Instituto Madrileño de Estudios Avanzados en Alimentación, Madrid, Spain; ⁶⁵ Department of Public Health and Clinical Medicine, Section for Medicine, Umeå University, Umeå, Sweden; ⁶⁶ Dean's Office, University of Kentucky, Lexington, KY; ⁶⁷ Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA; ⁶⁸ Division of Genetics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; ⁶⁹ Broad Institute of MIT and Harvard, Cambridge, MA; ⁷⁰ The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Copenhagen, Denmark; ⁷¹ Department of Production Research and Innovation, Regionshuset, Sorø, Denmark; ⁷² Department of Laboratory Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA; ⁷³ Tulane University Obesity Research Center, Tulane University, New Orleans, LA.

* Address correspondence to this author at: Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, 1440 Canal St., New Orleans, LA 70112. E-mail lqi1@tulane.edu; luqi@hsph.harvard.edu.

† T. Huang, M. Ding, H.K.M. Bergholdt, B.G. Nordestgaard, C. Ellervik, and L. Qi contributed equally to this work.

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